UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS

SEP 9 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **DICAMBA**: Request for New Chronic Toxicity/Carcinogenicity Study in Rats - A Follow-Up to the HED RfD Committee's Recommendations.

FROM: Jess Rowland, M.S., Acting Section Head 9/6/96
Section I, Toxicology Branch II, Health Effects Division (7509C)

TO: **Robert Taylor / Vickie Walters**
Product Manager 25
Registration Division (7505C)
and
Sherell Sterling / Jane Mitchell
Reregistration Division (7508W)

THRU: Yiannakis Ioannou, Ph.D., Acting Chief 9/6/96
Toxicology Branch II, Health Effects Division (7509C)

PC Code: 029801 Tox.Chem. No. 295
Registrant: Sandoz Agro Inc.

DATA PACKAGE IDENTIFICATION: Submission: S459483 DP Barcode: D229544

SUMMARY: The Reference Dose (RfD) Committee of the Health Effects Division (HED) met on February 1, 1996 and determined that the chronic toxicity study in dogs, the chronic toxicity/carcinogenicity study in rats, and the carcinogenicity study in mice were inadequate and not acceptable for regulatory purposes since in all three species, the highest doses tested were not adequate to assess either the chronic toxicity or the carcinogenic potential of dicamba. The Committee recommended that *"the respective toxicology branch will determine if any new studies will be required"*.

An *ad hoc* Committee consisting of the toxicologist and the Branch Chief's of the two Toxicology Branches as well as the Science Analysis Branch met to respond to the RfD Committee's recommendations. Based on the *ad hoc* Committee's conclusions, Toxicology Branch II is recommending the following: (i) a new chronic toxicity/carcinogenicity study be conducted with dicamba. The dose levels to be used in this study should be selected based on the results of a 90-day dietary study as well as consultation with the Agency; (ii) although a new carcinogenicity study in mice is not requested at this time, a final decision will be made after evaluation of the results of the new rat study; (iii) a new chronic study in dog is not needed.

I. BACKGROUND

The Reference Dose (RfD) Committee of the Health Effects Division (HED) met on February 1, 1996 reviewed the toxicology data base for dicamba and established an RfD of 0.45 mg/kg/day. During this review, the Committee also determined that the chronic toxicity study in dogs (MRID No. 40321102), the chronic toxicity/carcinogenicity study in rats (MRID Nos. 00125333/00146150), and the carcinogenicity study in mice (MRID No. 40872401) were inadequate and do not satisfy Subdivision F guideline requirements §83-1b, 83-2a/83-5 and 83-2b, respectively. These studies were determined to be unacceptable since in all three species, the highest doses tested were not adequate to assess either the chronic toxicity or the carcinogenic potential of dicamba. Because of the lack of adequate long-term studies, the Committee concluded that dicamba should be classified as a Group D Carcinogen; Not Classifiable as to Human Carcinogenicity. The Committee recommended that *"the respective toxicology branch will determine if any new studies will be required"* (See attached RfD/Peer Review Report of Dicamba, dated July 29, 1996).

II. RESPONSE BY THE TOXICOLOGY BRANCH

An *ad hoc* Committee consisting of the toxicologist (J. Rowland), Branch Chief's of Toxicology Branch I (K. Baetcke), Toxicology Branch II (M. Ioannou), and the Science Analysis Branch (W. Burnam) met on July 31, 1996 to respond to the RfD Committee's recommendation.

a. §83-1b Chronic Toxicity Study in Dogs

The RfD for dicamba is based on the NOEL of 45 mg/kg/day established in the 2-generation reproduction study. In the unacceptable dog study (MRID No. 40321102), no systemic toxicity was seen at the highest dose tested (NOEL = >52 mg/kg/day). Since the results of a new study will not yield a NOEL lower than that seen in rats in the 2-generation reproduction study upon which the RfD is based, the *ad hoc* Committee determined that a new study in dogs is not required.

b. §83-a (83-5) Chronic Toxicity/Carcinogenicity Study in Rats

The *ad hoc* Committee concurred with the RfD Committee that in the chronic toxicity/carcinogenicity study (MRID No. 0012533/00146150), the highest dose tested (2500 ppm or 125 mg/kg/day) was not adequate to assess either the chronic toxicity or the carcinogenicity of dicamba. There was no systemic toxicity at this dose; the NOEL was >2500 ppm. In addition, no rationale was provided for the selection of the dose levels (0, 50, 250 or 2500 ppm) tested. Therefore, the *ad hoc* Committee concluded that a new study must be conducted at higher doses and these doses should be selected based on the results of a 90-day toxicity study.

c. §83-b Carcinogenicity Study in Mice

The RfD Committee did not concur with the NOEL (1000 ppm) and the LOEL (3000 ppm) established in the Data Evaluation Report (HED Doc. No. 007141) and determined that the NOEL should be 3000 ppm with an LOEL not established. The Committee recommended that an Executive Summary be written to reflect these changes. Following is the revised Executive Summary:

> In a carcinogenicity study (MRID No. 40872401), CD-1 mice (52/sex/dose) received diets containing dicamba (technical, 86.8%) at 0, 50, 150, 1000 or 3000 ppm for 89 weeks (males) or 104 weeks (females). Treatment had no adverse effect on survival, body weight, body weight gain, food consumption, hematology parameters, organ weights, or gross or histopathology. At the dose levels tested there was no evidence of carcinogenicity. However, the RfD Committee concluded that due to the lack of systemic toxicity, the dose levels tested were not adequate to assess the carcinogenic potential of dicamba in male or female CD-1 mice. Under the conditions of this study the NOEL is >3000 ppm (HDT); a LOEL was not established.
>
> This study is classified as **unacceptable** and does not satisfy the Subdivision F guideline requirement §82-2b for a carcinogenicity study in mice.

The *ad hoc* Committee concurred with the RfD Committee that the highest dose tested (3000 ppm or 450 mg/kg/day) was not adequate to assess the carcinogenic potential of dicamba. There was no systemic toxicity at this dose; the NOEL was >3000 ppm. Inspite of the lack of systemic toxicity, the *ad hoc* Committee, noted that the highest dose used in this study was approximately half the Limit-Dose (7000 ppm or 1000 mg/kg/day) and therefore determined that a new study may not be necessary at this time. A final decision on this will be made upon evaluation of the results of the new study in rats.

III. CONCLUSIONS

The Toxicology Branch is requesting that a new chronic toxicity/carcinogenicity study be conducted with dicamba. The dose levels to be used in this study should be selected based on the results of a 90-day dietary study as well as consultation with the Agency. Although a new carcinogenicity study in mice is not requested at this time, a final decision will be made after evaluation of the new rat study. A new chronic study in dogs is not needed.

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JUL 29 1996

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of **DICAMBA:** 2-Methoxy-3,6-dichlorobenzoic acid, or 3,6-dichloro-o-anisic acid.

CASRN --1918-00-9
EPA Chem;. Code:
Caswell Number: 295

FROM: Henry W. Spencer, Ph.D. 7/24/96
Member, RfD/Peer Review Committee
SAB
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/Peer Review Committee
SAB
Health Effects Division (7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

The Health Effects Division RfD/Peer Review Committee met on August 10, 1995 and on February 1, 1996 to discuss and evaluate the toxicology data submitted in support of the reregistration of Dicamba and assess an RfD value for the chemical. The second meeting of the Committee was to discuss additional information on the reproductive and developmental toxicity of the chemical.

Material available for review consisted of data evaluation records (DERs) for chronic feeding/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a chronic (one-year) feeding study in dogs **(83-1b)**, a chronic (two-year) feeding study in dogs **(83-1b)**, a three-generation reproduction study in rats **(83-4) and** a two-generation reproduction study in rats **(83-4)**, a developmental toxicity study in rats **(83-3a)** and two developmental toxicity studies in rabbits. An acute

another dog study is to be required to evaluate the toxicity of Dicamba.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the combined chronic toxicity study in rats and though considering the DER to be adequate, considered the study to be inadequate for evaluating the carcinogenic potential of Dicamba in rats. The mouse study was also considered by the Committee to have not been tested at high enough dosages to evaluate carcinogenicity in the mouse. The Committee concluded that Dicamba should be classified as a Group D carcinogen based on the lack of both rat and mouse bioassays being tested at high enough levels to induce any significant toxicity in the two different species. The respective Toxicology branch will determine if any new studies will be required.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (MRID No. 00028249; HED Doc. Nos. 007745, 004036) to be of poor quality and not adequate to evaluate the reproductive toxicity in the study. The Committee considered it to be supplementary or unacceptable. A second reproductive toxicity study in rats (MRID No.43137101; HED Doc. No.011391) was considered to be acceptable and the DER was adequate. The NOEL for systemic toxicity in the parents was 1500 ppm (136 mg/kg/day) and a LOEL was 5000 ppm (450 mg/kg/day) based on tense/stiff body tone and slow righting reflex and increased relative liver to body weights in both generations. Reproductive toxicity was manifested as decreased pup growth in all generations and matings at 1500 ppm (136 mg/kg/day) with a NOEL of 500 ppm (45 mg/kg/day).

A developmental toxicity study in rats (MRID Nos. 00084023, 00084024; HED Doc. No. 004036) was submitted. The DER was found to be lacking in detail and the Committee considered that the study should be rereviewed. A Developmental toxicity study in rabbits (MRID No. 42429401; HED Doc. No. 010617) was submitted and was considered by the Committee to be an acceptable study however, the DER would be considered to be adequate when the executive summary was rewritten in the new format and a table of observations was updated. The effects noted in the DER included a maternal NOEL of 30 mg/kg/day from capsule dosing: an LEL of 150 mg/kg/day based on abortions and clinical signs, ie. decreased body weight and body weight gains, and decreased food consumption. A developmental toxicity NOEL was established at 150 mg/kg/day and the LOEL of 300 mg/kg/day was based on irregular ossification of the nasal bones of the skull. An earlier rabbit developmental study (MRID No. 00028236; HED Doc. No. 004036) was down-graded from core-minimum to core-supplementary and has been superseded by MRID No. 42429401.

At the second meeting of the Committee on February 1, 1996 was

results of this study (rigid body tone, slightly impaired righting reflex and impaired gait) the LOEL was established at 12000 ppm (767.9 mg/kg/day) and 1028.9 mg/kg/day)in males and females respectively. The NOEL was established at 401.4 mg/kg/day and 472 mg/kg/day in males and females respectively. Both studies and DERs of the neurotoxicity studies were considered to be adequate and acceptable for regulatory requirements.

F. Establishing RfD

The Committee considered the various study data and the LOEL and NOELs established from those studies. The Committee concluded that of the many studies, the most appropriate on which to base the RfD was the 2-generation reproduction study in rats (MRID No. 43137101). The study exhibited an LOEL and NOEL of 450 mg/kg/day and 136 mg/kg/day respectively for the systemic toxicity in the parental animals and 136 mg/kg/day and 45 mg/kg/day respectively for the LOEL and NOEL for reproductive toxicity in the pups as significantly decreased pup growth in all generations and matings above 45 mg/kg/day. Therefore, using the NOEL of 45 mg/kg/day and an uncertainty factor of 100, a Reference Dose (RfD) of 0.45 mg/kg/day is established for Dicamba. This RfD supersedes the previous RfD of 0.03 mg/kg/day.

G. Individuals in Attendance:

Peer Review Committee members and associates present at the August 10, 1995 meeting were William Burnam (Chief, Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Sanju DiWan, Yung G. Yang, Kerry Dearfield, G. Reddy, Roger Gardner, Clark Swentzel, Stephen Dapson, Karl Baetcke (Chief, Tox Br 1), William Sette, Esther Rinde, Henry Spencer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Jess Rowland ----------

Clark Swentzel ----------

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Mike Ioannou ----------

CC: Stephanie Irene
Debra Edwards
Albin Kocialski
Mike Ioannou
Beth Doyle
Jess Rowland

data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rodents.

9. Hoberman, A. (1992). Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenicity Potential) Study of Technical Dicamba Administered Orally via Capsule to New Zealand White Rabbits. MRID No.42429401, HED Doc. No. 010617. Classification: minimum. This study satisfies the data requirement 83-3b for a developmental toxicity study in rabbits.

10.Goldenthal, E. I. and D. C. Jessup. (1978). Teratology Study in rabbits.MRID No. 00028236, HED Doc. No.004036, 011702. Classification: un- acceptable and superseded. This study does not satisfy data requirement 83-3b of the Subpart F of the Pesticide Assessment Guideline for a developmental toxicity study in rabbits.

11. Minnema,D. J. (1994). Subchronic Neurotoxicity Study of Dietary Technical Dicamba in Rats. MRID No. 43245210, HED Doc. No. 011493. Classification :guideline. This study satisfies data requirement 82-7 of the Subpart F of the Pesticide Assessment Guideline for a subchronic neurotoxicity study in the rat.

12. Minnema, D. J. (1993). Acute Neurotoxicity Study of Technical Dicamba by Gavage in Rats. MRID No. 42774104, HED Doc. No.01653. Classification: minimum. This study satisfies data requirement 81-8 of the Subpart F of the Pesticide Assessment Guideline for an acute neurotoxicity study in the rat.